Refer to: Ocular complications of rheumatic diseases—Medical Staff Conference, University of California, San Francisco. Calif Med 118:17-22, May 1973

Medical Staff Conference

Ocular Complications of Rheumatic Diseases

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* *It is important for the internist to recognize the local manifestations of systemic illnesses. This may allow for earlier diagnosis and therefore choice of appropriate therapy. At times the local complications may be of great importance in the patient's disability. Finally, an understanding of the pathogenesis of such complications may help to elucidate the pathogenesis of the associated disease. The eye is an accessible organ which not infrequently reflects systemic illness. Today Dr. Wallace V. Epstein will describe for us some of the ocular complications which may occur in the course of rheumatic diseases.*

DR. EPSTEIN:* Almost without exception patients with chronic inflammatory intraocular disease are subjected to general health examinations in an effort to find some systemic illness which might help explain the chronic inflammation within the eye. If one reads a great many of the letters of

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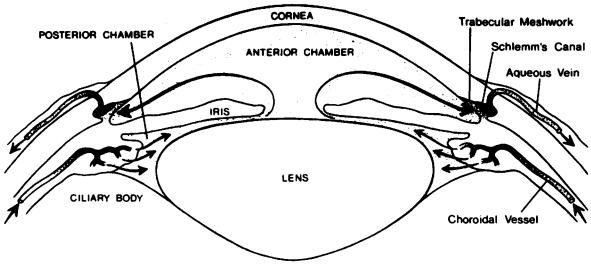

Figure 1.—Cross-section of anterior segment of eye, showing aqueous circulation from synthesis in ciliary body to outflow through canal system of the anterior chamber angle.

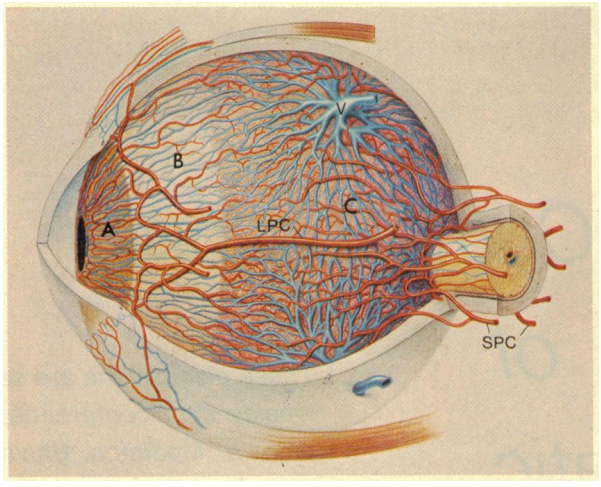

Figure 2.—Vascular circulation of the uveal tract to the choroid, (C) ciliary body (B) and iris (A). Anastomosis of long (LPC) and short (SPC) ciliary vessels is shown. Vortex vein (V) is also shown.

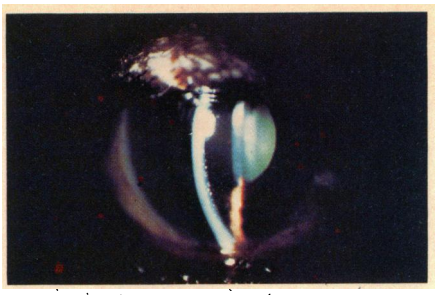

Figure 3.—Slit-lamp appearance of keratitic precipitates on corneal endothelium (on concave edge of center arc). Anterior chamber (dark area) separates corneal reflex from illuminated iris and lens.

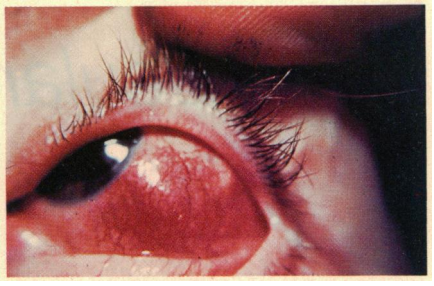

Figure 4.—Nodular episcleritis of rheumatoid arthritis illustrating intense hyperemia of episcleral vessels.

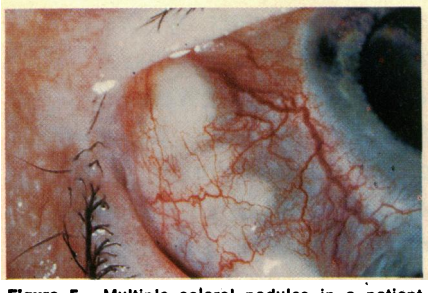

Figure 5.—Multiple scleral nodules in a patient with peripheral rheumatoid arthritis. Scleral thinning and hyperemic scleritis are also shown.

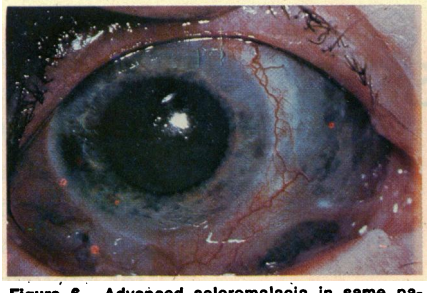

Figure 6.—Advanced scleromalacia in same patient as in Figure 5, showing blue choroid pigment and vasculature through thinned sclera.

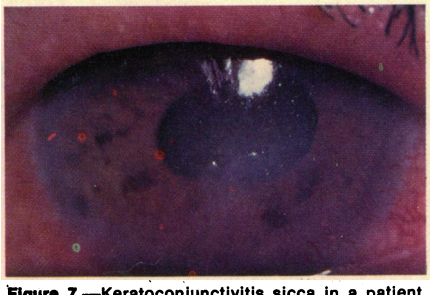

Figure 7.—Keratoconjunctivitis sicca in a patient with Sjögren's syndrome, showing filamentous keratitis manifest by irregularity and fragmentation of corneal light reflex. Note corneal filaments and edematous clouding of the cornea.

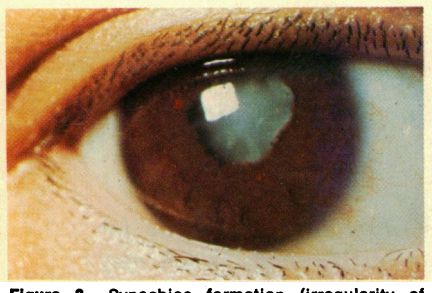

Figure 8.—Synechiae formation (irregularity of pupil margin) and cataract formation (white pupil) in a patient with juvenile rheumatoid arthritis.

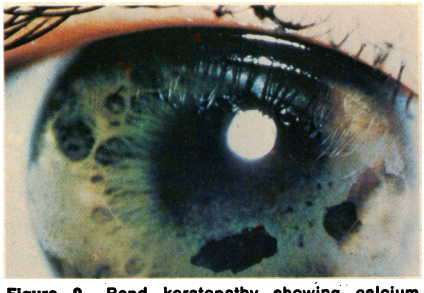

Figure 9.—Band keratopathy showing calcium disposition in the subepithelial layer of the cornea in a patient with juvenile rheumatoid arthritis. Note characteristic "Swiss cheese" appearance.

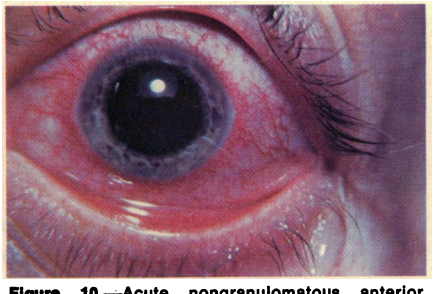

Figure 10.—Acute nongranulomatous anterior uveitis in a patient with ankylosing spondylitis. Note perilimbal ciliary flush and hyperemia of episcleral vessels.

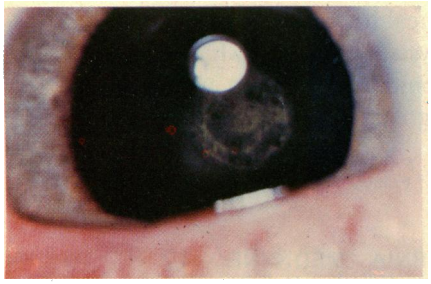

Figure 11.—Posterior subcapsular cataract in a patient with ankylosing spondylitis whose iridocyclitis was treated with topical adrenocorticosteroids.

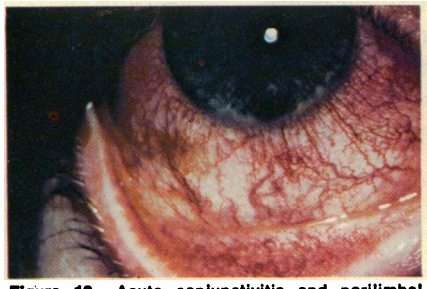

Figure 12.—Acute conjunctivitis and perilimbal vessel engorgement in a patient with Reiter's syndrome.

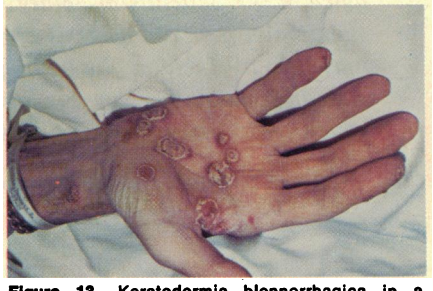

Figure 13.—Keratodermia blennorrhagica in a patient with acute Reiter's syndrome.

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consultation to the referring ophthalmologist, it becomes clear that the patient might be better served if the questions raised by the ophthalmologist were more limited and if the general health work-up and diagnostic search performed by the internist were more directed toward specific related etiologic conditions associated with the various forms of intraocular disease. The frequent association of acute and chronic intraocular inflammation with the rheumatic diseases furnishes the basis for my special interest and will provide the source for the illustrations.[1]

A very brief review of ocular anatomy[2] reminds us that the term *anterior segment disease* refers to disease involving portions of the eye including and anterior to the ciliary body while *posterior segment* disease refers to disorders located in the part of the eye posterior to the ciliary body. The iris itself divides the anterior segment into an anterior and posterior aqueous chamber. The strong association of particular etiologic factors with inflammation originating in or showing preponderance in one or another location make these anatomic boundaries important. (See Figure 1.)

The distribution and the presentation of the inflammatory process is closely correlated with the vascular pattern of the uveal tract and of the retina as well as the circulation of the aqueous. Aqueous, synthesized in the ciliary body, flows through the posterior chamber and anteriorly past the pupillary margin of the iris into the anterior chamber to reenter the vascular system by way of the canal system of the anterior chamber angle. (See Figure 2.)

Several of the inflammatory diseases to be illustrated herein are associated with obstruction to aqueous flow by inflammatory adhesions (synechiae) of the iris to the lens at the pupillary edge and by diminished aqueous outflow. Both obstruction to aqueous flow through the pupil into the anterior chamber and decreased outflow at the anterior chamber angle can lead to the development of glaucoma. Diminished aqueous synthesis due to inflammation of the ciliary body may result in hypotony. The ciliary body and the outflow canal system bear a resemblance to the functions of the synovial membrane and its several functions for the joint cavity. This similarity may provide insights into the frequent association of anterior segment eye disease and some forms of synovitis.

The vascular circulatory system of the uveal tract is a second circulation separate from the retinal circulation within the eye, and a knowledge of it helps us to understand the patterns of the various inflammatory disease states. The uveal tract itself consists of the iris, ciliary body and choroid. Its vascular supply arises, as does the central retinal artery, from the ophthalmic branch of the internal carotid artery. The uveal tract vasculature derived predominately from the long and short ciliary vessels provides a path by which anterior segment disease may extend to involve the back of the eye through the choroidal portion of the uveal circulation. The reverse process may also occur. The uveal and the retinal circulations are without mutual anastomosis of blood vessels or lymphatics, thus helping to explain choroiditis without retinitis, and vice versa. Uveitis or inflammation of the iris, ciliary body and the choroid may present clinically as diseases of the vitreous, lens, or aqueous as well as of the scleral coat of the eye which communicate with the uveal tract circulation. Iridocyclitis, as seen in juvenile rheumatoid arthritis and in adult ankylosing spondylitis, follows the continuity of the uveal circulation in the sequential appearance of iritis, cyclitis and, rarely, choroiditis. Corneal disease also follows anatomic planes, with the keratitis of juvenile rheumatoid arthritis and the keratoconjunctivitis of the sicca-Sjögren's syndrome appearing in the sub-epithelial and epithelial layer, while the keratopathy of syphilis begins deep in the cornea close to the corneal endothelium. Unfortunately, adequate examination of the cornea and the anterior chamber is not possible with the ophthalmoscope alone. The corneal and anterior chamber structures on slit lamp examination may reveal keratitic precipitates on the corneal endothelium and cells and protein (flare) in the anterior chamber (Figure 3.) All of these would probably be missed if examination were done by ophthalmoscope alone. The corneal and anterior chamber disease of juvenile rheumatoid arthritis demands regular slit-lamp examination, as does the iridocyclitis of ankylosing spondylitis.

A predominately anterior chamber uveitis (Table 1) tends to be associated with diseases such as ankylosing spondylitis and the iridocyclitis associated with juvenile rheumatoid arthritis,[3] while predominately posterior uveal tract inflammation[4] should suggest toxocariasis, histoplasmosis, toxoplasmosis, sarcoidosis or syphilis. In addition to the diagnostic significance of the primary site of the inflammation, the distinction between granulomatous and nongranulomatous inflamma-

TABLE 1.—*Types of Uveitis According to Site of Predominant Inflammatory Disease*

Anterior Segment
(a) Juvenile rheumatoid arthritis
(b) Ankylosing spondylitis
(c) Sarcoid
(d) H. zoster
(e) Syphilis

Posterior Segment
(a) Toxoplasmosis
(b) Syphilis
(c) Sarcoidosis
(d) Toxocariasis
(e) Histoplasmosis

Both Segments
(a) Tuberculosis
(b) Sarcoidosis
(c) Toxoplasmosis

TABLE 2.—*Changes in Incidence of Presumptive Etiologic Factors in Granulomatous Uveitis During the Period 1941 to 1967**

	1941 percent	1944 percent	1953 percent	1965 percent	1967 percent
Tuberculosis	79	52	23	4	1
Syphilis	16	17	7	0	1
Toxoplasmosis ...	0	0	26	27	18
Histoplasmosis ...	0	0	0	22	22
Undetermined ...	0	6	18	39	26

*Modified from Schlaegel, T. F., Jr.,[8] p 27.

tion is important. Granulomatous disease is characterized by posterior or anterior chamber accumulations of macrophages that clear slowly. Nongranulomatous disease is associated with polymorphonuclear cells and lymphocytes in the anterior chamber and may clear rapidly with treatment. The iridocyclitis of ankylosing spondylitis typically has nongranulomatous cell accumulations in the anterior chamber while the cell accumulations of sarcoidosis and toxoplasmosis are typically called granulomatous. It has been my observation that what may be called nongranulomatous disease at one time may be called granulomatous at another stage; however, even such inconstant hints should be grasped by the consulting physician. Granulomatous diseases tend to involve the entire uveal tract while nongranulomatous diseases tend to be limited to the anterior segment, to be acute in onset, and to be painful because of involvement of the ciliary body. The nongranulomatous iridocyclitis associated with juvenile rheumatoid arthritis is an exception in that it is frequently progressive yet painless.

The eye diseases associated with adult peripheral rheumatoid arthritis range from episcleritis or scleritis[5] to nodule formation with resultant scleromalacia.[6] This disorder is generally limited to rheumatoid arthritics with high levels of serum rheumatoid factor and usually is associated with subcutaneous rheumatoid nodules. Rheumatoid scleronodular disease illustrates the spread of the inflammatory process from the coats of the eye to the anterior chamber where a protein flare and cells are seen on slit-lamp examination. At times the posterior segment also may be involved in a retinal detachment. Figure 4 shows an example of rheumatoid nodular episcleritis in a patient who had not had active synovitis for several years. This is a not uncommon observation concerning many of the extra-articular manifestations of rheumatoid arthritis. Figure 5 shows scleritis and multiple scleral rheumatoid nodules and illustrates the perilimbal inflammation of scleritis. Episcleritis and conjunctivitis tend to be more superficial and not localized to the perilimbal area. The extension of the rheumatoid nodule within the scleral coat results, at times, in significant anterior and posterior segment disease by virtue of its anatomic proximity to these other areas. The end stage of rheumatoid nodular scleritis results in scleral thinning and exposure of the choroid, and eventually may cause scleromalacia perforans. (Figure 6)

In the keratoconjunctivitis sicca related to Sjögren's syndrome[7] we are able to see several manifestations of keratitis detectable by changes in the surface corneal light reflex. (Figure 7) The light reflex is irregular and fragmented, with clear disturbances of the epithelial layer. Patients with keratoconjunctivitis sicca show conjunctivitis and superficial keratitis; and, with further fragmentation and loosening of the epithelial layer, filaments are formed and the picture of filamentous keratopathy is seen. An unusual but tragic final consequence of this process may be corneal ulceration and perforation.

When we turn from nongranulomatous forms of ocular inflammation closely related to systemic diseases such as rheumatoid arthritis or ankylosing spondylitis to granulomatous uveal tract inflammation, we find a vast array of changing associations. The pattern of presumptive diagnoses of granulomatous uveitis has changed over the years, as is shown in Table 2.[8] It is interesting to note that in 1941 tuberculosis was thought responsible for 79 percent of cases of granulomatous uveitis and none were of undetermined cause, while in 1967 the undetermined cause group rose to 26 percent, and tuberculosis was thought responsible for only 1 percent.

The onset of anterior nongranulomatous uveitis in a child must immediately raise the question of juvenile rheumatoid arthritis (JRA). Characteristically the child has little overt inflammation or pain, and the uveitis may first be detected by the mother as variation in the pupil color (cataract), pupil irregularity due to binding of the iris margin to the anterior surface of the lens—synechiae—(Figure 8) or visual disturbance. At times the uveitis may precede the onset of overt synovitis or systemic manifestations of JRA such as fever or the characteristic rash. A complication of the uveitis of JRA, but not limited to this childhood uveitis, is the formation of a corneal band developing just beneath the corneal epithelium. (Figure 9) The calcium salt deposition may lead to vision loss when it develops in the visual axis and may be cleared by chelation after removing the superficial epithelium. A recent report by Schaller and coworkers[10] suggests an immunologic process as part of the uveitis of JRA. She reported that serum IgG antinuclear antibody is found in 88 percent of juvenile rheumatoid arthritics with chronic iridocyclitis and in only 29 percent of JRA patients without uveitis. The possibility is raised that it may be possible to predict the emergence of the ocular complication of JRA. Despite meticulous care, this eye disease of the juvenile arthritic has a grave outlook: 40 of 61 patients reported upon by Schaller and coworkers had major vision loss, blindness developing in 18 patients and secondary glaucoma in 15.[11]

In adults, anterior nongranulomatous uveitis, especially in men, frequently is associated with ankylosing spondylitis. It is remarkable that of the diseases commonly damaging the sacro-iliac joints (Table 3) all but osteoarthritis and osteitis condensans ilii have an associated ocular complication. Unlike patients with juvenile rheumatoid arthritis with anterior uveitis, adults with anterior nongranulomatous uveitis usually present with a red, painful eye. Figure 10 illustrates typical episcleritis of ankylosing spondylitis. Slit-lamp examination reveals significant anterior uveitis with spill-over of inflammatory cells into the anterior vitreous.

Recurrences of this uveitis associated with spondylitis may result in cellular deposits on the endothelial surface of the cornea (keratitic precipitates) and at the iris margin (Koeppe nodules), leading to synechiae with obstruction to aqueous flow and to the potential for developing glaucoma. Both the inflammatory process and a side effect of corticosteroid therapy may contribute to the formation of posterior subcapsular cataracts. (Figure 11) Management of these serious complications demands close cooperation between ophthalmologist and internist. It is of interest that ophthalmology has it own method of diagnosing spondylitis in that Verhoeff's test for spondylitis[8] is declared positive when the patient is unable to extend the cervical vertebrae well enough to put his chin on the chin-rest of the slit-lamp apparatus.

TABLE 3.—*Conditions Leading to Sacro-Iliitis*

1. Ulcerative colitis	5. Psoriasis
2. Reiter's disease	6. Whipple's disease
3. Ankylosing spondylitis	7. Osteoarthritis
4. Regional enteritis	8. Osteitis condensans ilii

The ocular complications of Reiter's syndrome may precede or may follow the genital and arthritic manifestations of this disorder.[13] Conjunctivitis occurs in about one-third of cases and may precede or present simultaneously with iritis, as illustrated in Figure 12. Also shown is an example of the keratodermia blennorrhagica found in about 10 percent of cases of the Reiter's syndrome. (Figure 13)

Diagnosis of the rheumatic diseases that present with or may precede ocular disorders depends, for the most part, on clinical rather than laboratory criteria. Except for the regular association of high levels of serum rheumatoid factor with the sclerodular disease of rheumatoid arthritis,[14] there are no serological procedures that reflect directly on the process of inflammation involvement. The association of serum antinuclear antibody with the uveitis of JRA and the association of high serum levels of antibody to double stranded ribonucleic acid in some adult patients[15] with idiopathic uveitis may provide insights into etiologic and pathogenetic processes in these disorders. Other studies have indicated that immunologic reactions of the delayed hypersensitivity type directed toward uveal tract antigens are operative in several forms of uveitis including sympathetic ophthalmia.[16] The search continues for laboratory procedures which will reflect directly on the level of the intraocular inflammatory process in order to allow better-informed regulation of drug therapy.[17]

Although unquestionably desirable, effective management of the associated rheumatic disorder fails to insure an equally satisfactory response of the ocular inflammation. Both JRA and ankylosing spondylitis show poor correlation of the degree of

joint inflammation with ocular inflammation. The identification of infectious processes, especially those associated with posterior granulomatous uveitis, offers the greatest opportunity for definitive therapy. The special association of uveitis with several of the rheumatic diseases continues to offer a provocative challenge for future research.

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ACKNOWLEDGMENTS

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